

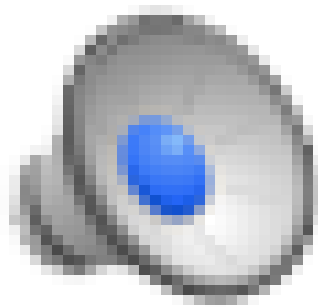
# How the basal ganglia generate behavior

Henry Yin  
Duke University

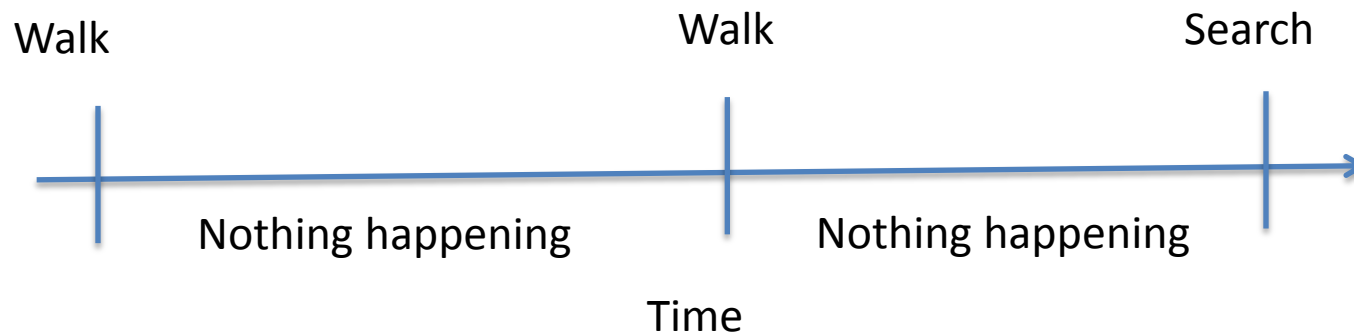
# Outline

- A new approach to studying behavior in freely moving mice.
- Relationship between basal ganglia activity and behavior.
- A new model of basal ganglia function.

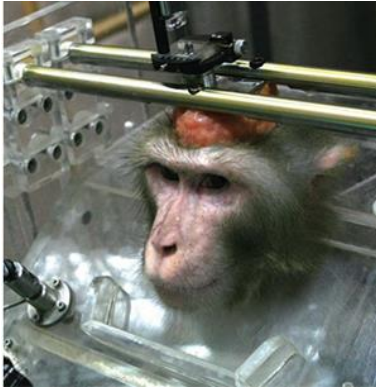
# How do we study behavior?



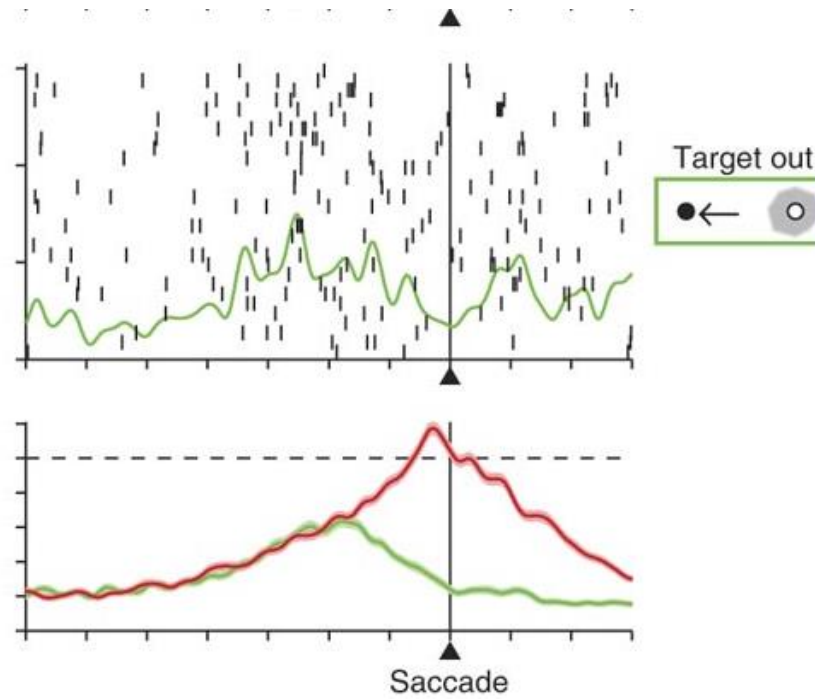
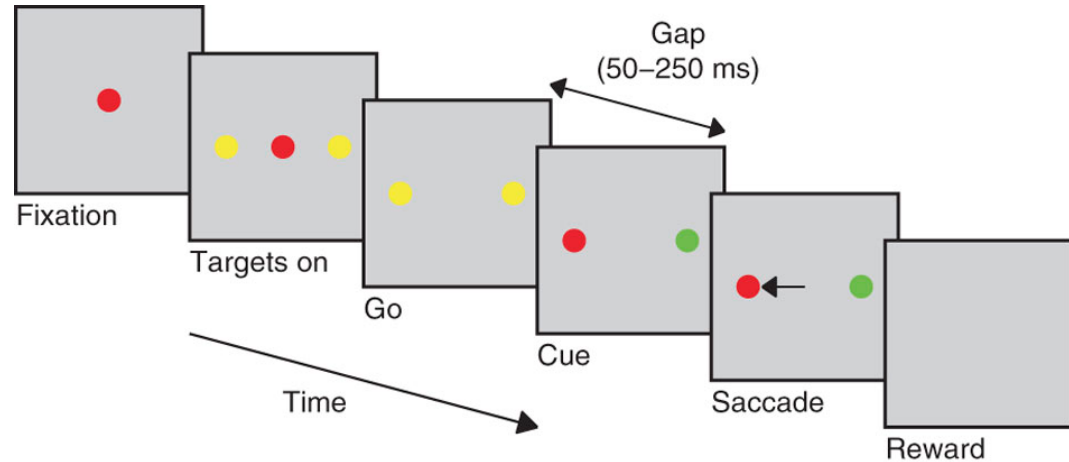
## Traditional event-based approach



# Event-based approach in neuroscience



H. Esteky

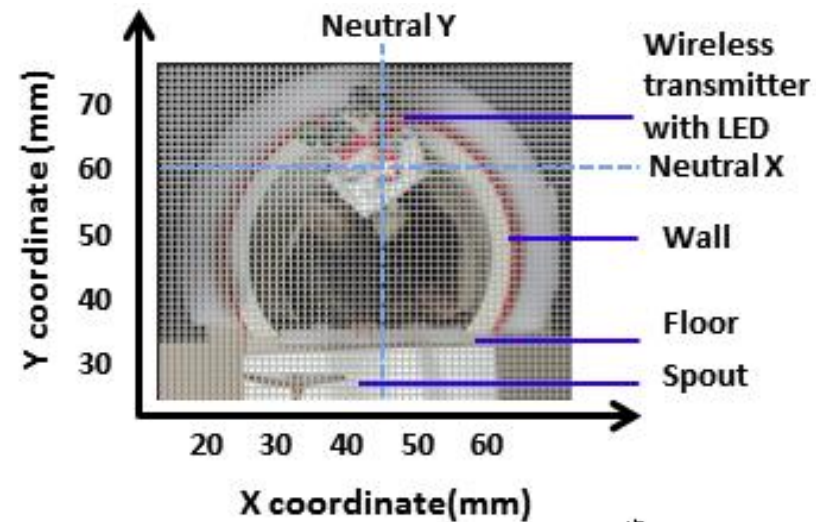


E. Salinas

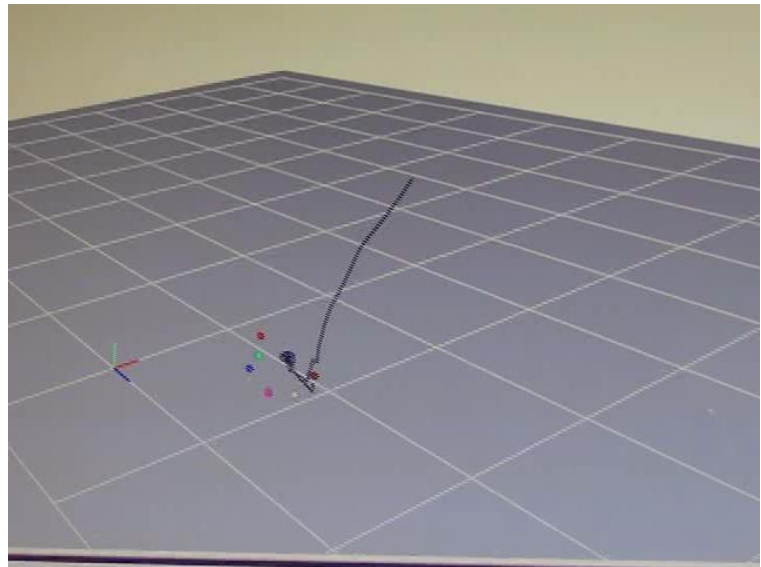
# Process-based approach

## 2D video

Position in Cartesian coordinates : (x, y)

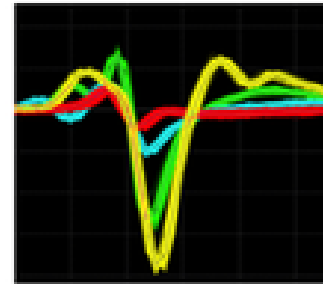


## 3D motion capture



# Measuring and manipulating neural activity in freely moving mice

## Wireless recording



## Wireless optogenetics



Stimulation  
software

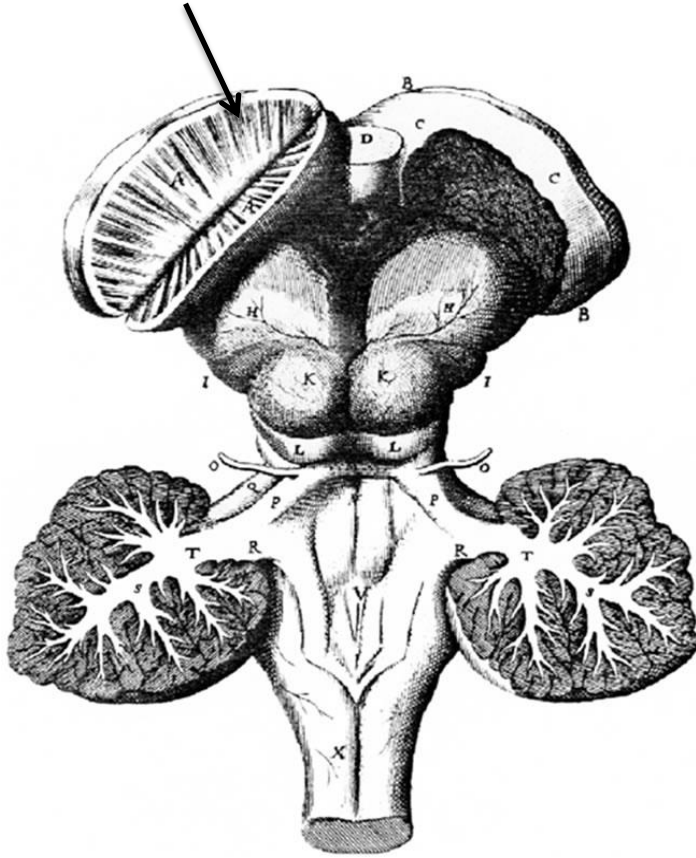


Transceiver



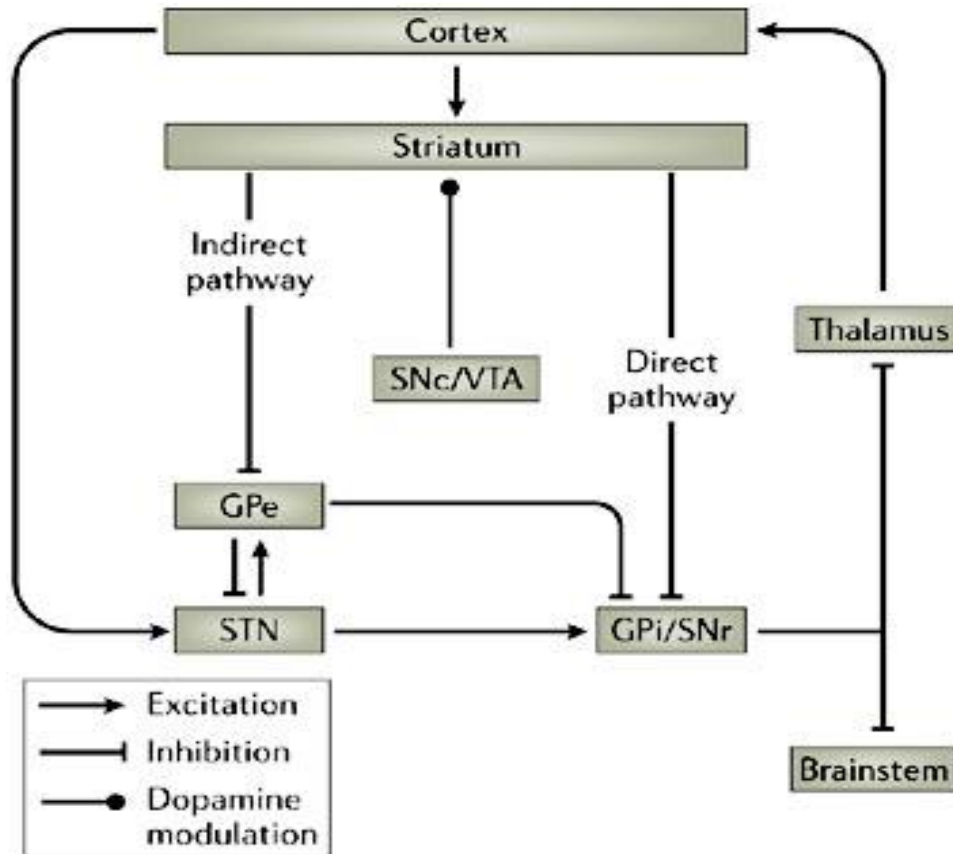
# What are the basal ganglia?

Corpus striatum (illustrated by Christopher Wren 1664)



- Willis, 1664: critical for movement
- Burdach, 1826: critical for volition
- Implicated in most psychiatric and neurological disorders.
- Complete removal of the cerebral cortex at birth does not abolish voluntary behavior but complete BG lesion abolished voluntary behavior (Bjursten et al 1976, Sorenson and Ellison 1970).

# Standard model of the BG



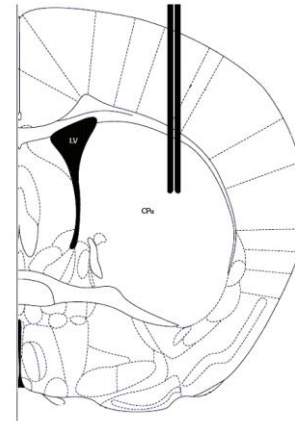
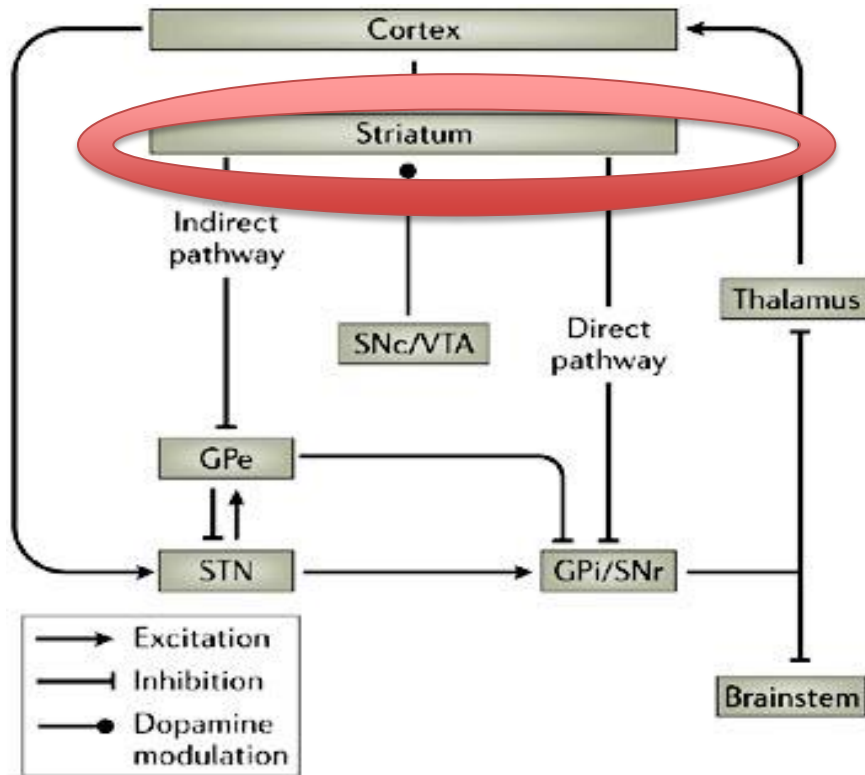
**GABAergic output inhibits behavior.**

**Reduction in output ‘opens the gate’ for behavior.**

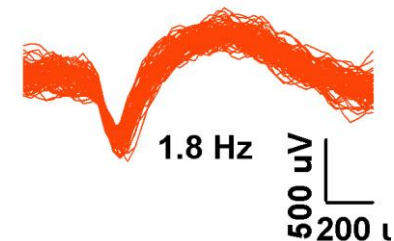
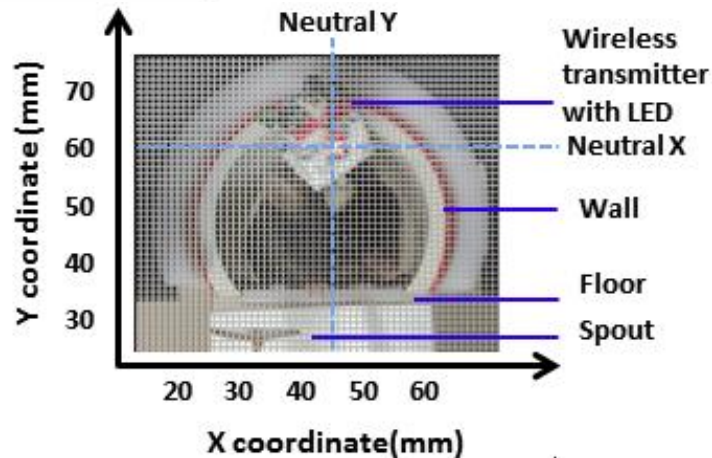
**Hypokinetic movement disorders (e.g. Parkinson’s): excessive BG output. “Rate model” (DeLong 1990).**



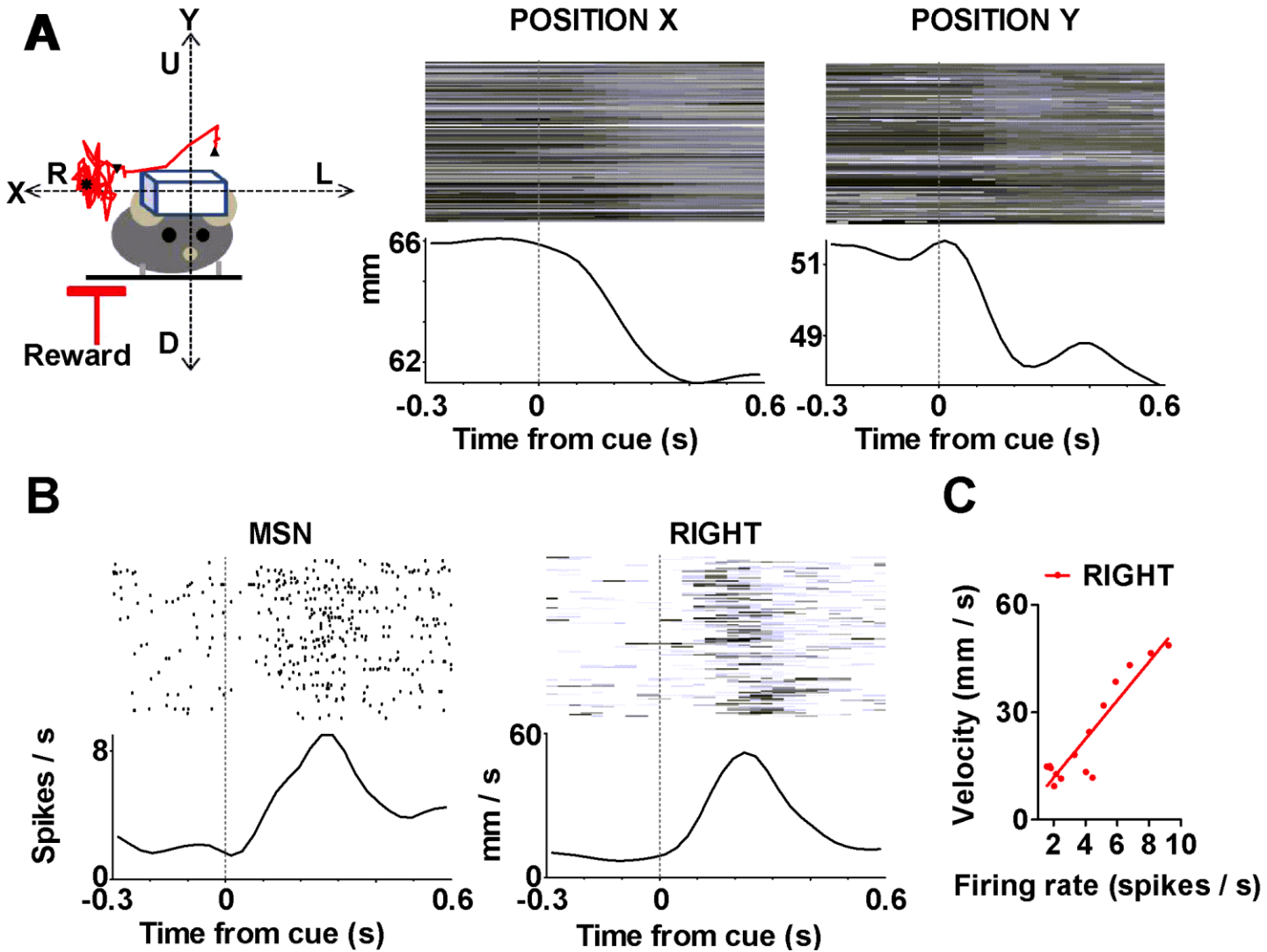
# Single unit recording from the sensorimotor striatum



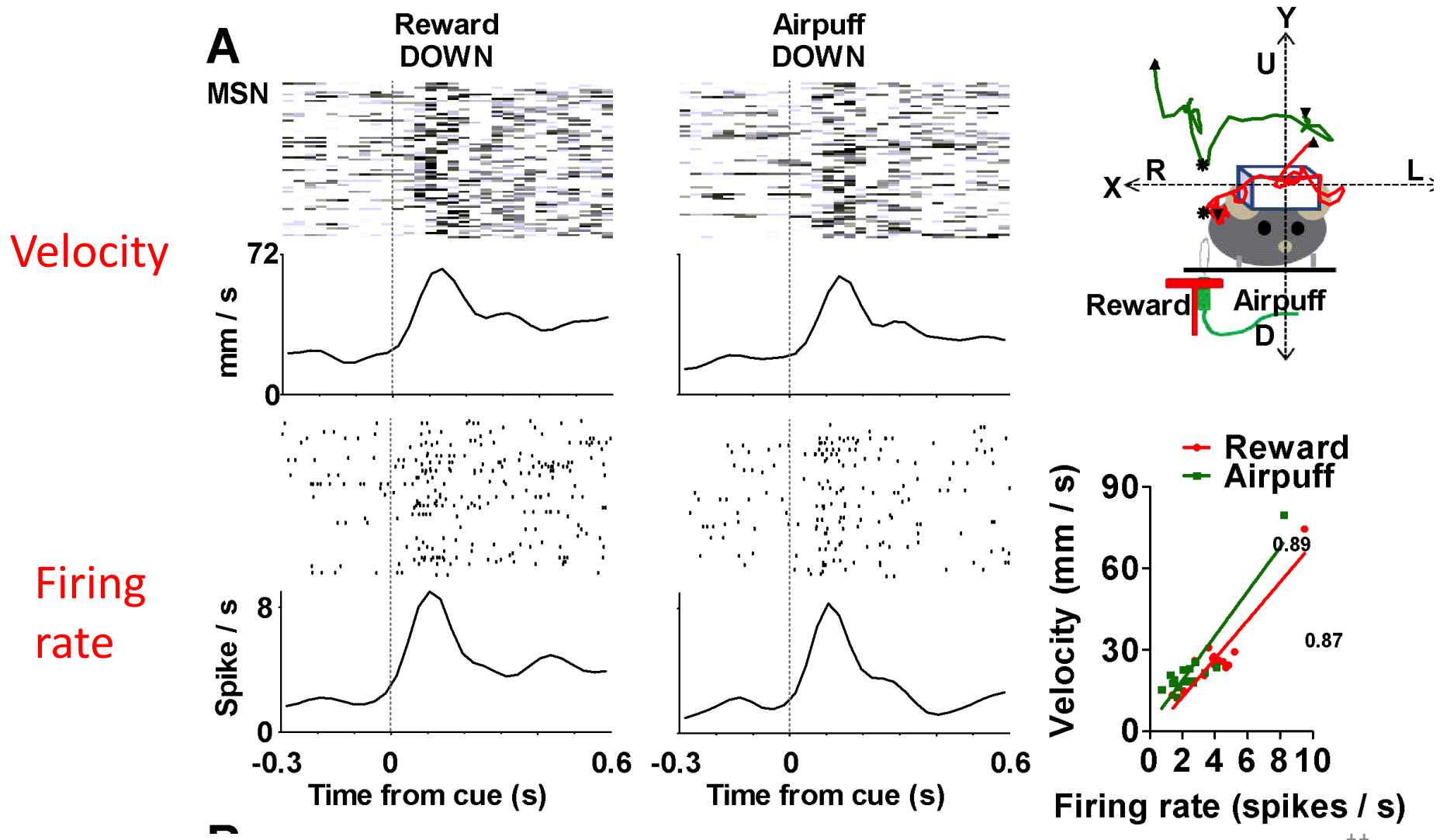
Medium spiny neuron



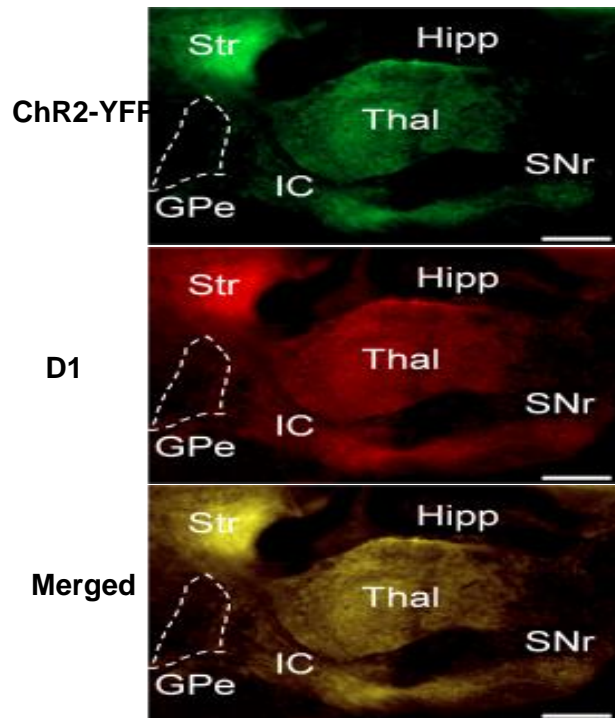
# Striatal output represents vector component of velocity



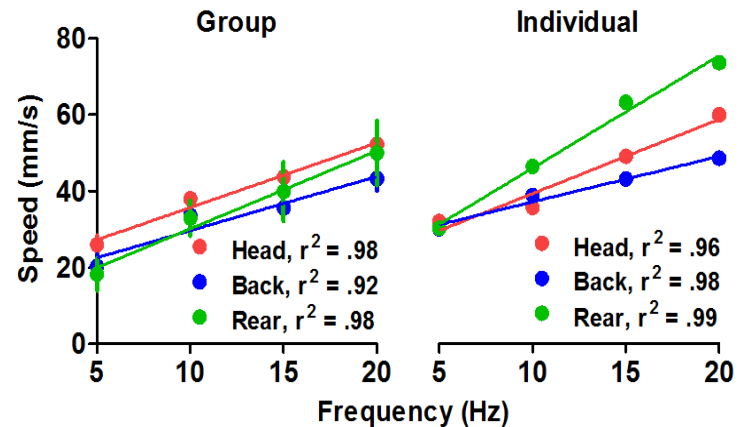
# Reward trials compared with air puff trials



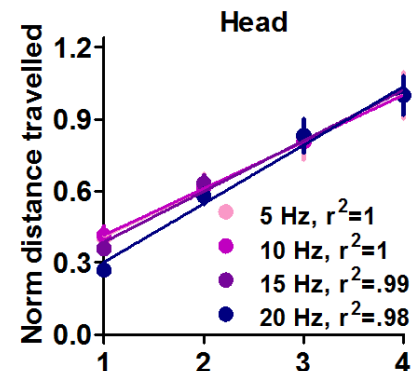
# Optogenetic stimulation of striatonigral pathway



## Stim frequency correlated with speed



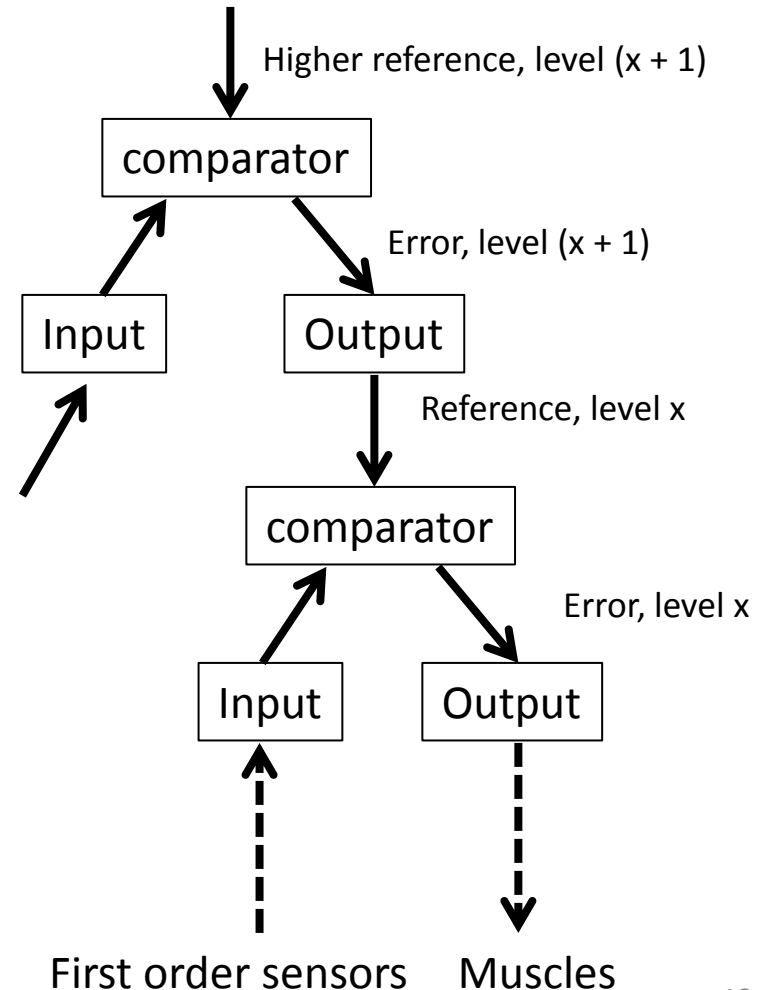
## Pulse number correlated with distance travelled



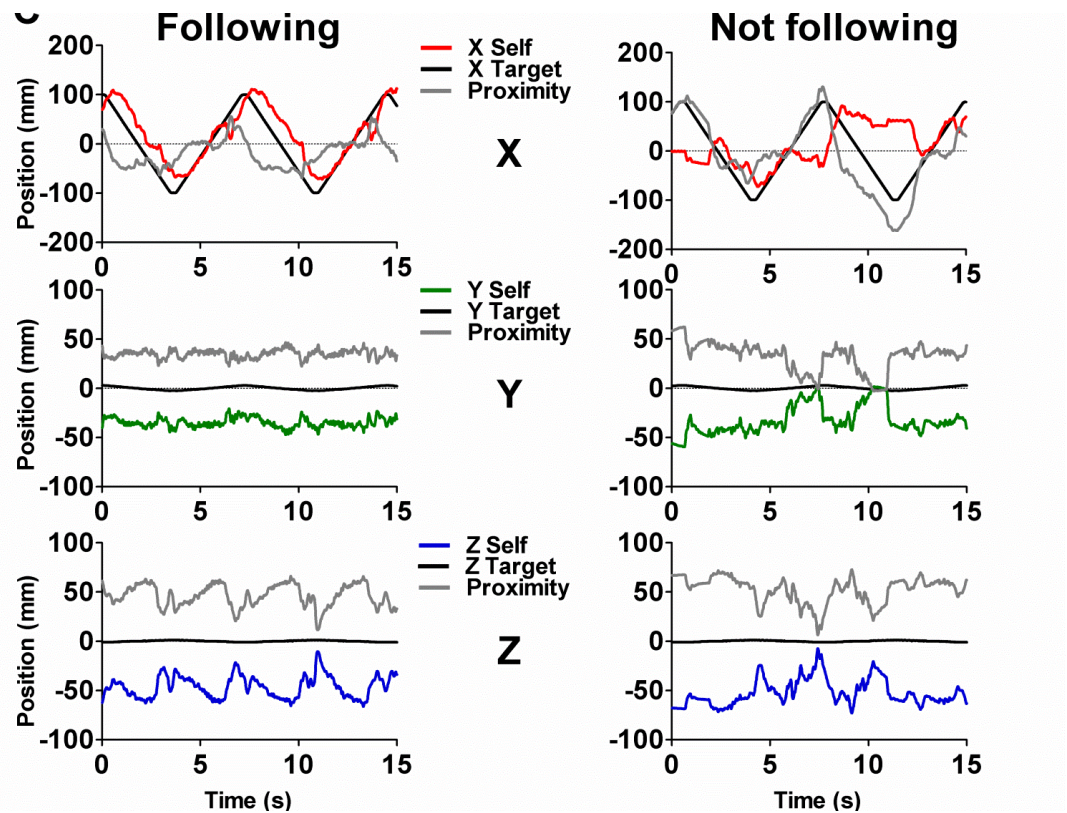
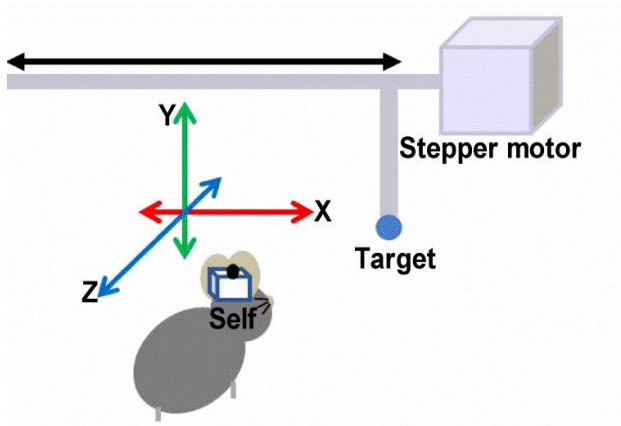
# Velocity control with negative feedback?

- Velocity or speed control (e.g. car).
- A general purpose controller: voluntary actions serve a number of different and acquired purposes, e.g. raising a hand.
- How to command this system?

## Hierarchical control of inputs

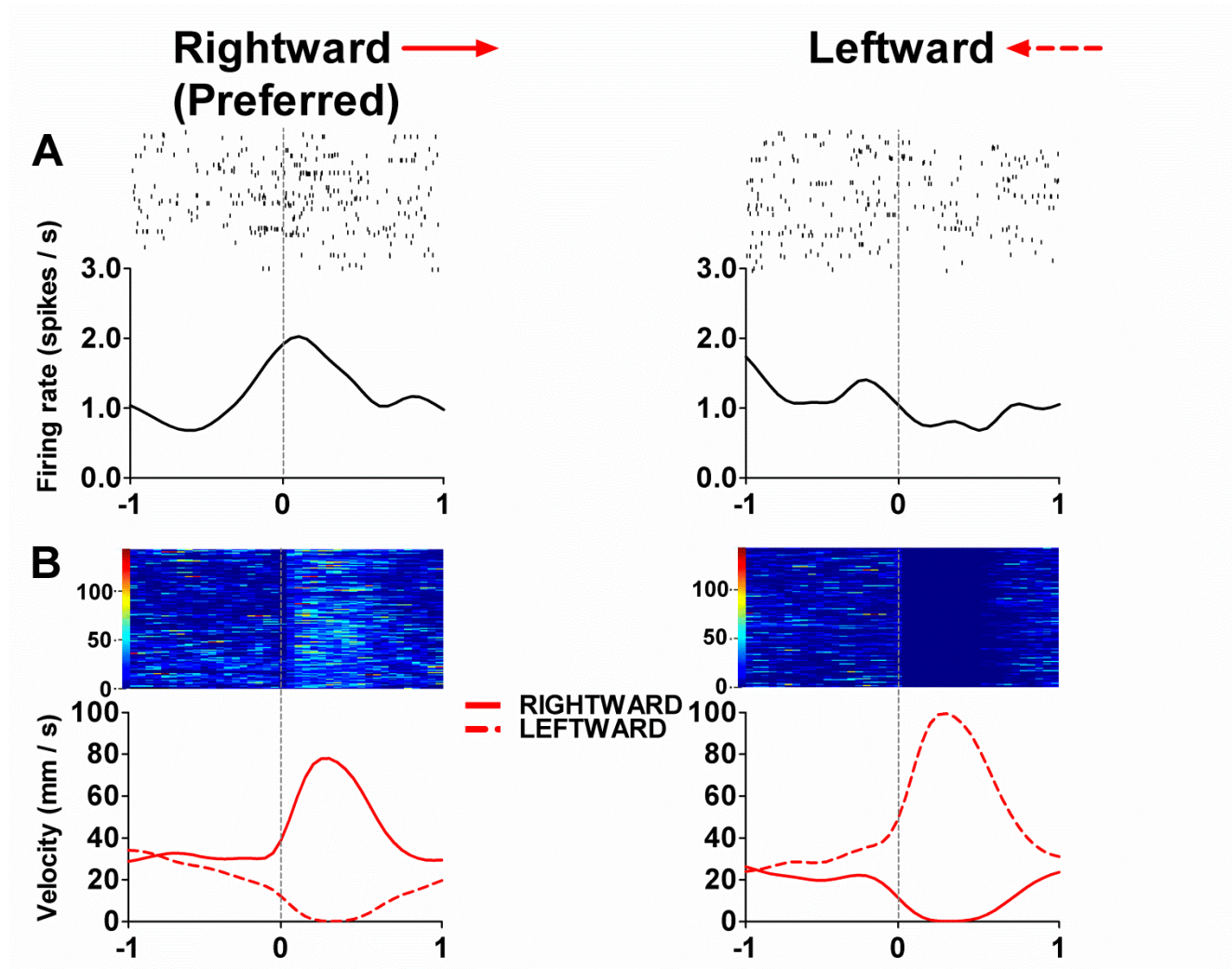


# Continuous reward tracking



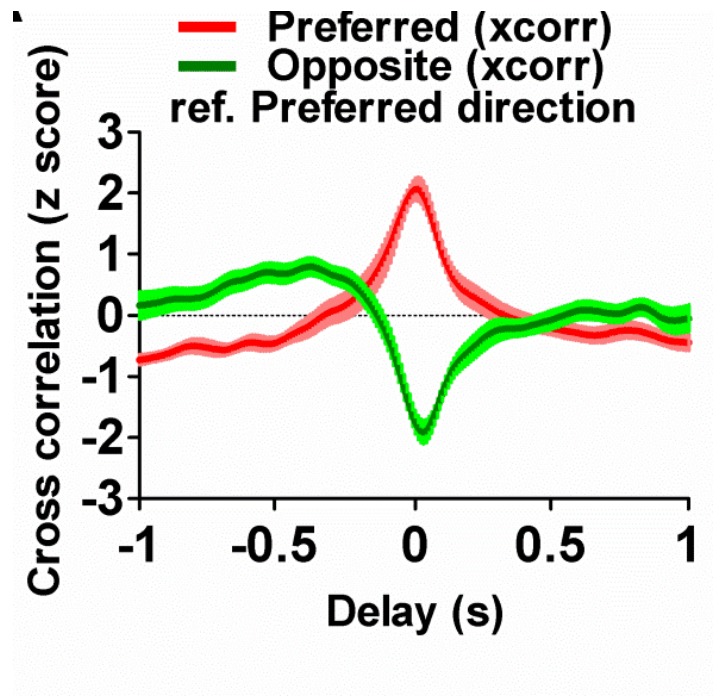


# Medium spiny projection neurons represent 6 directions of relative motion



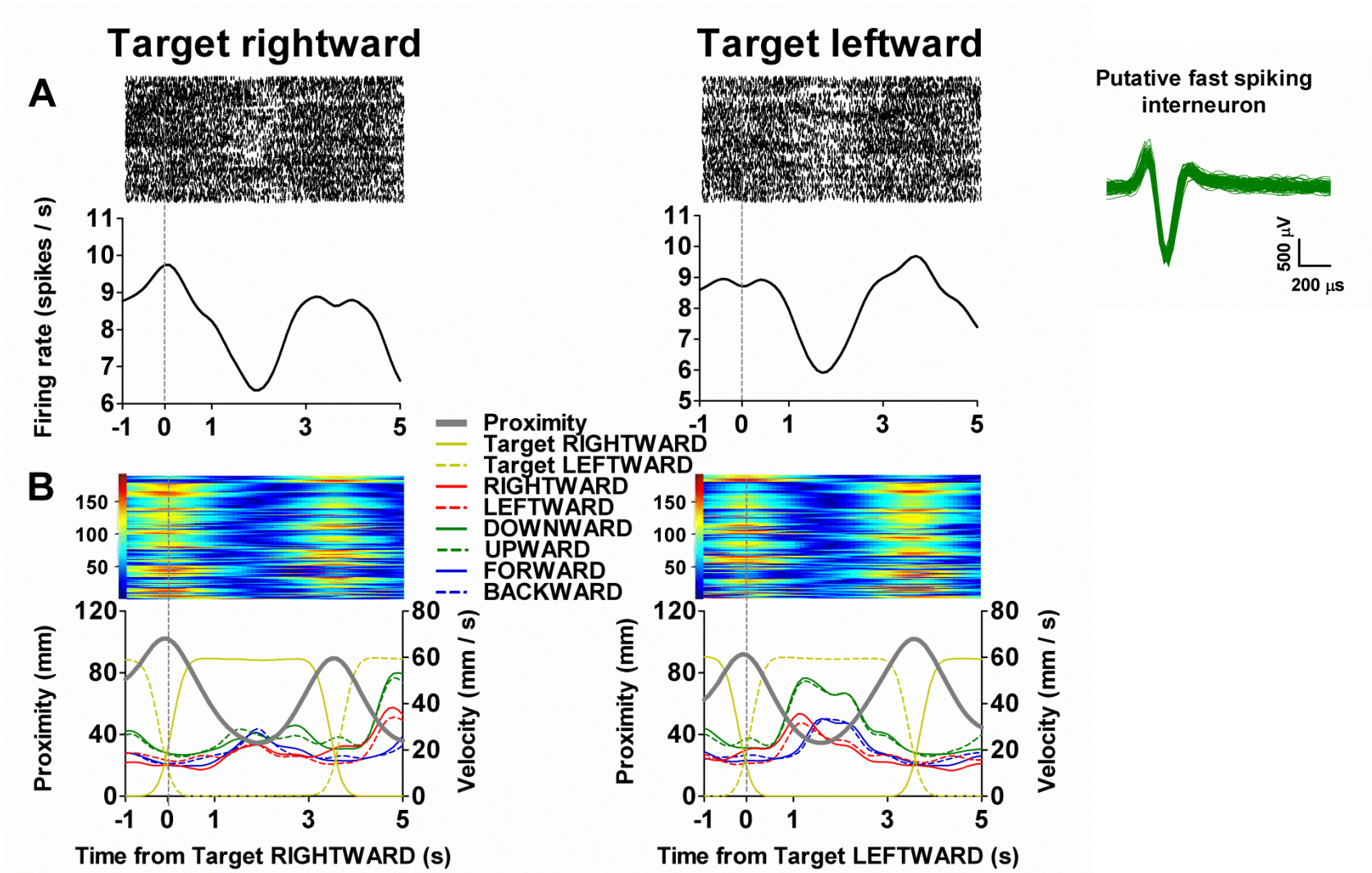
# Preferred direction vs. anti-preferred direction

- Positive correlation with velocity in the preferred direction but negative correlation with velocity in the opposite direction with a slight delay.
- Suggests reciprocal inhibition organization.

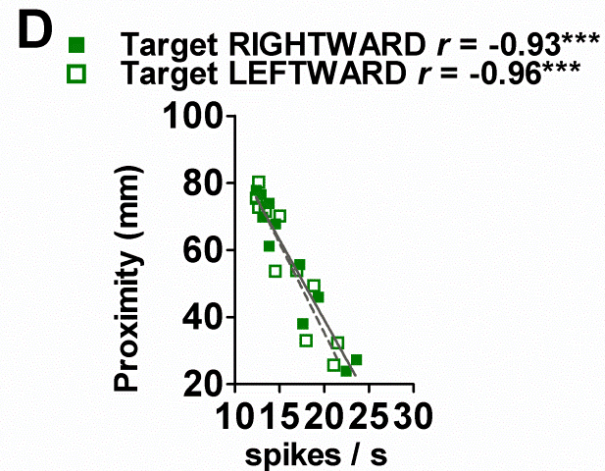
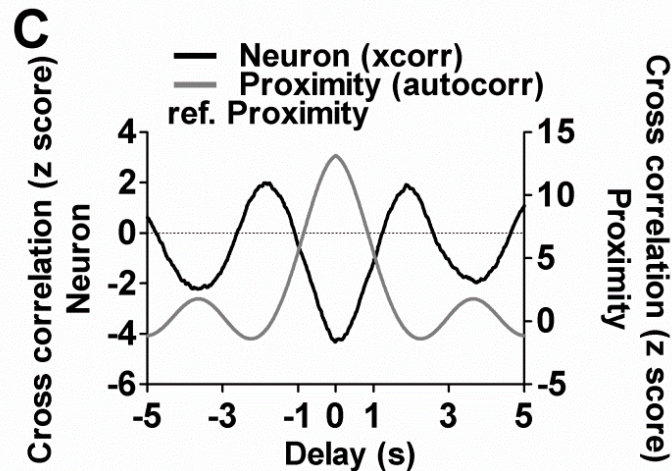
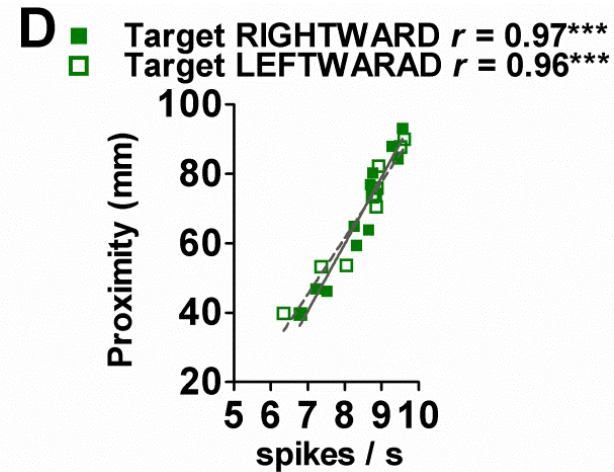
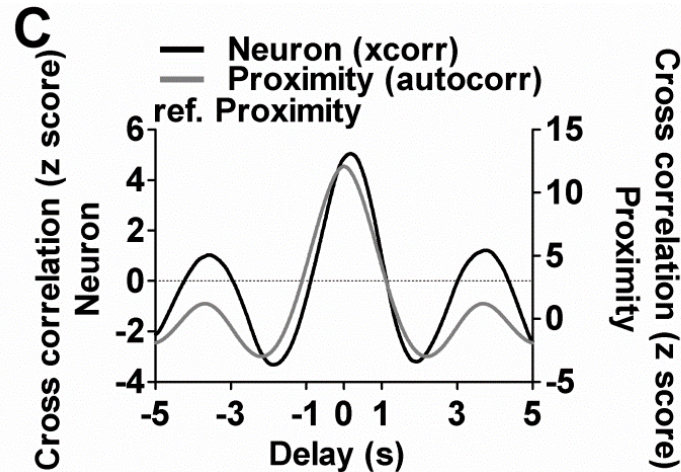




# Fast spiking interneurons signal goal proximity (tracking error)

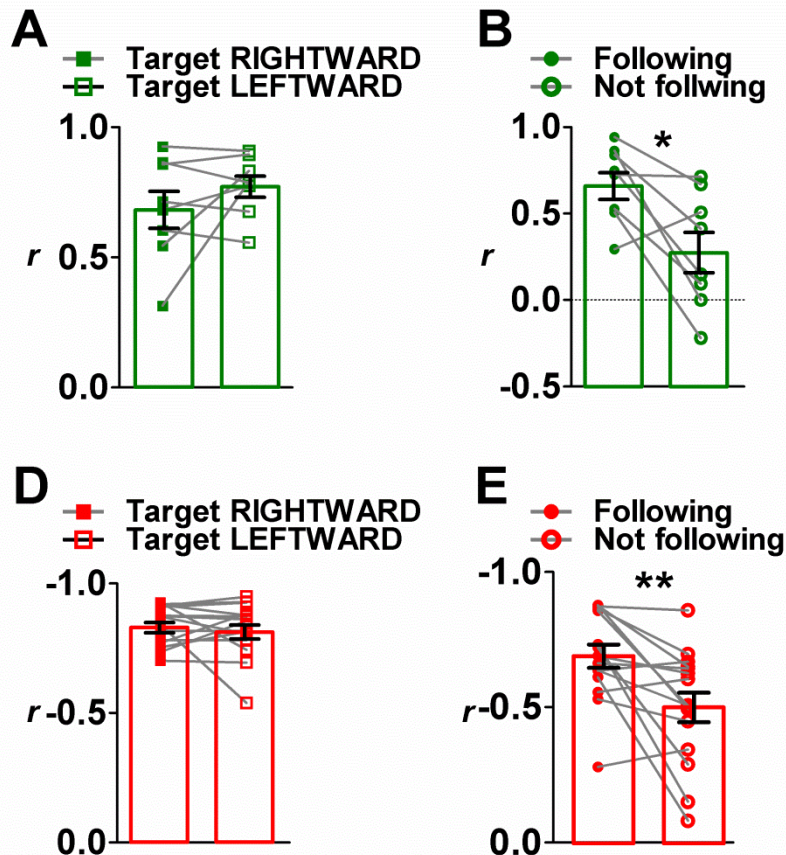


# Two opponent types of goal proximity neurons





# Goal proximity as tracking error

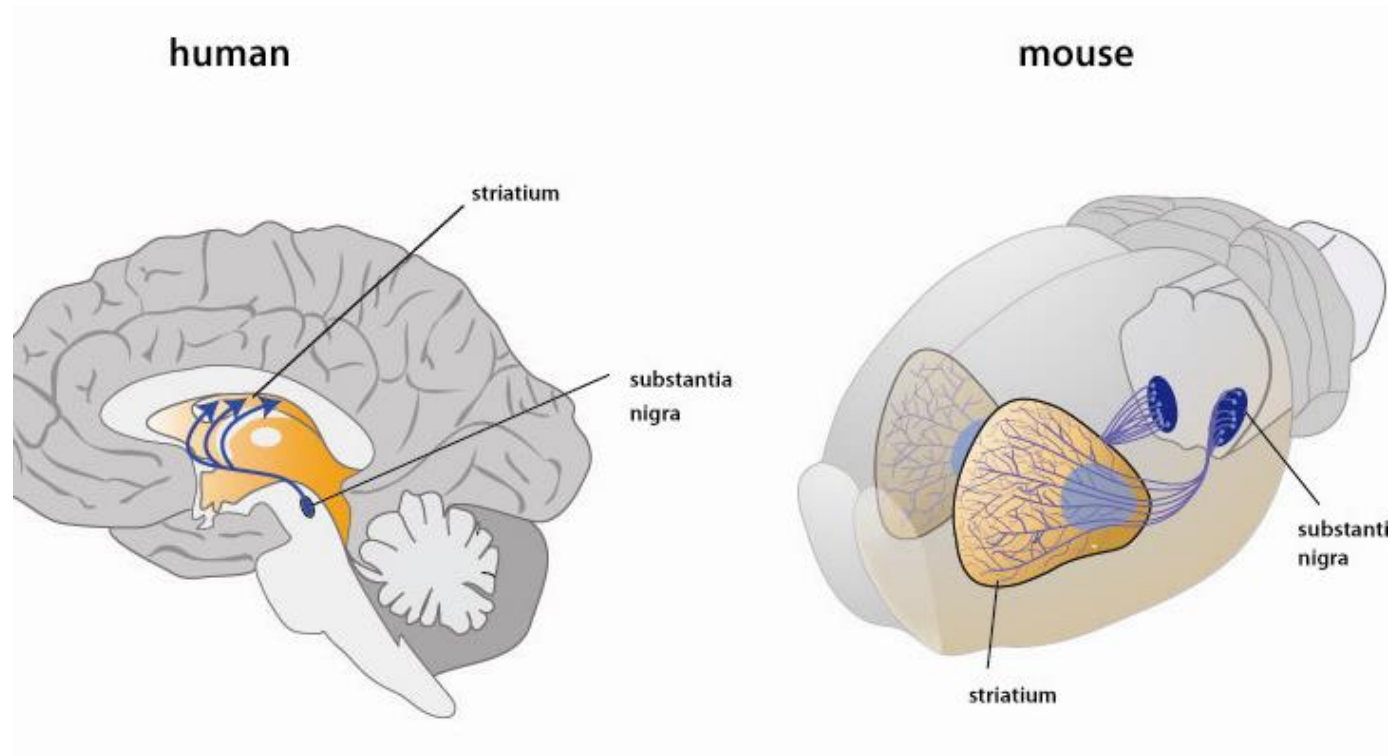


- Goal proximity representation independent of movement direction.
- Goal proximity representation degraded when not following target.

# Summary

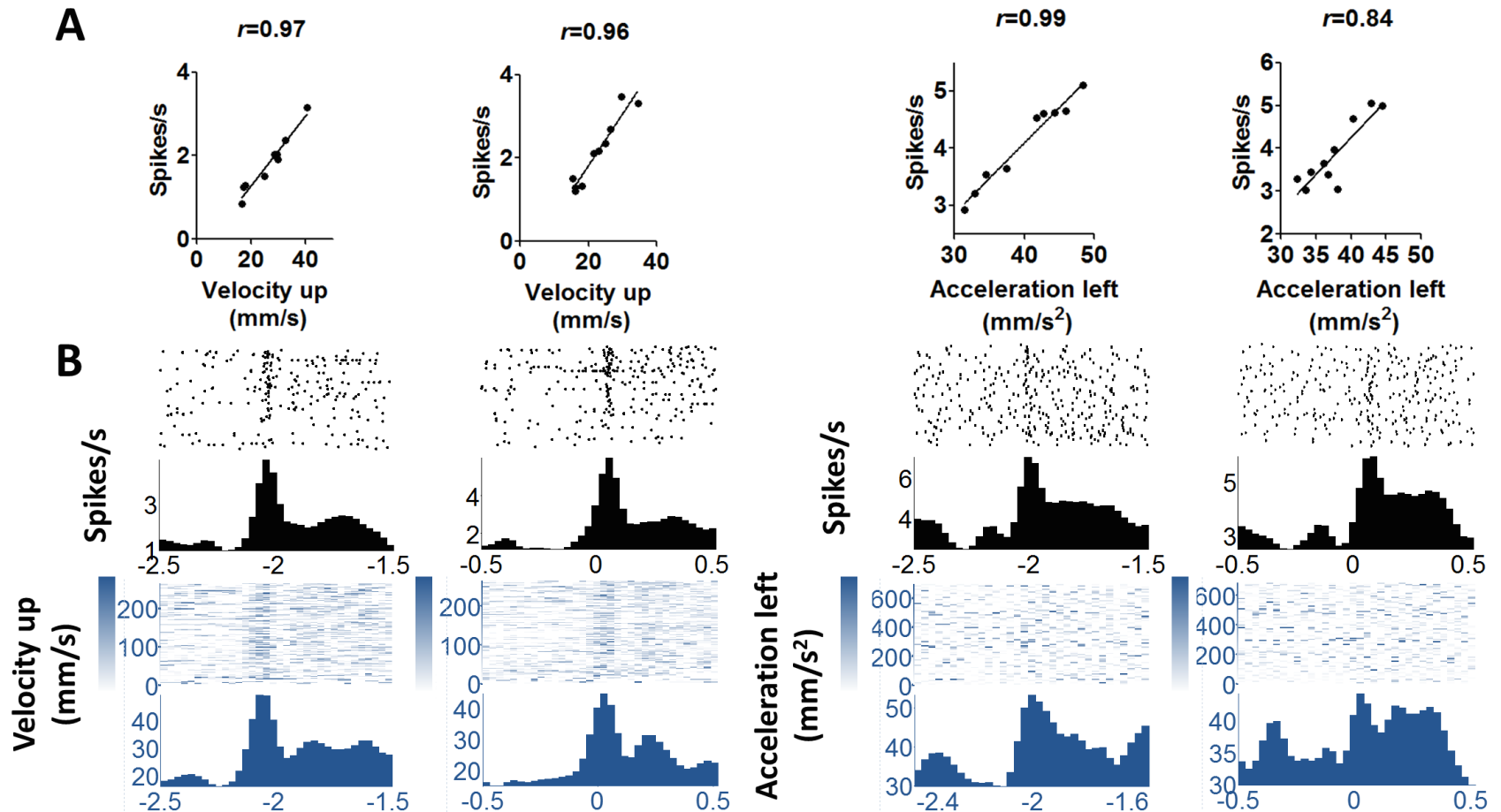
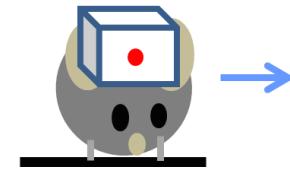
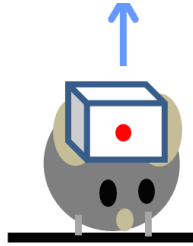
- MSNs represent comparator function in velocity controllers. Distinct vector components (x, y, z) corresponding to 6 directions of relative motion.
- Goal proximity (tracking error) represented by FSIs in sensorimotor striatum.

# Dopamine neurons

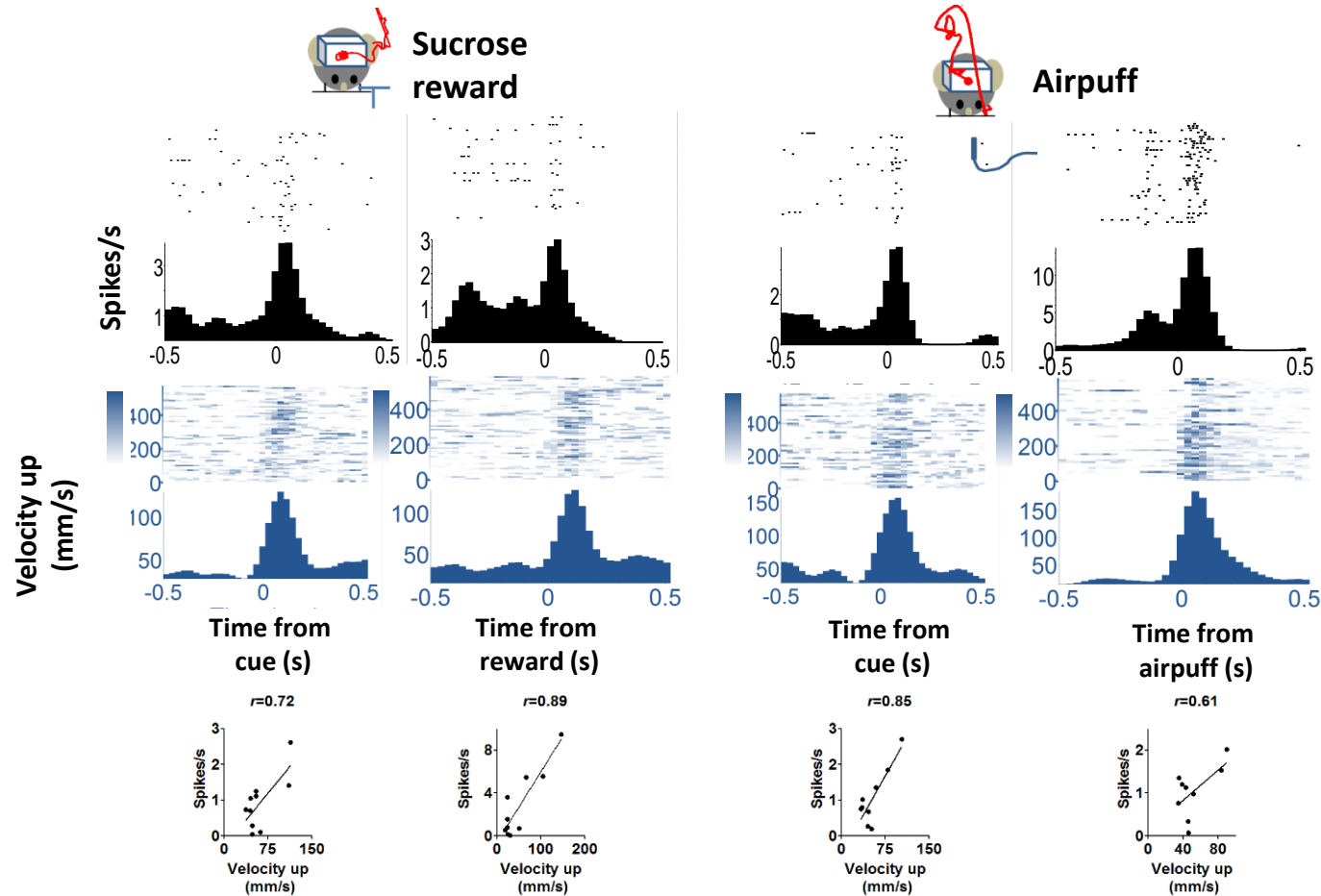


Edgar Kramer

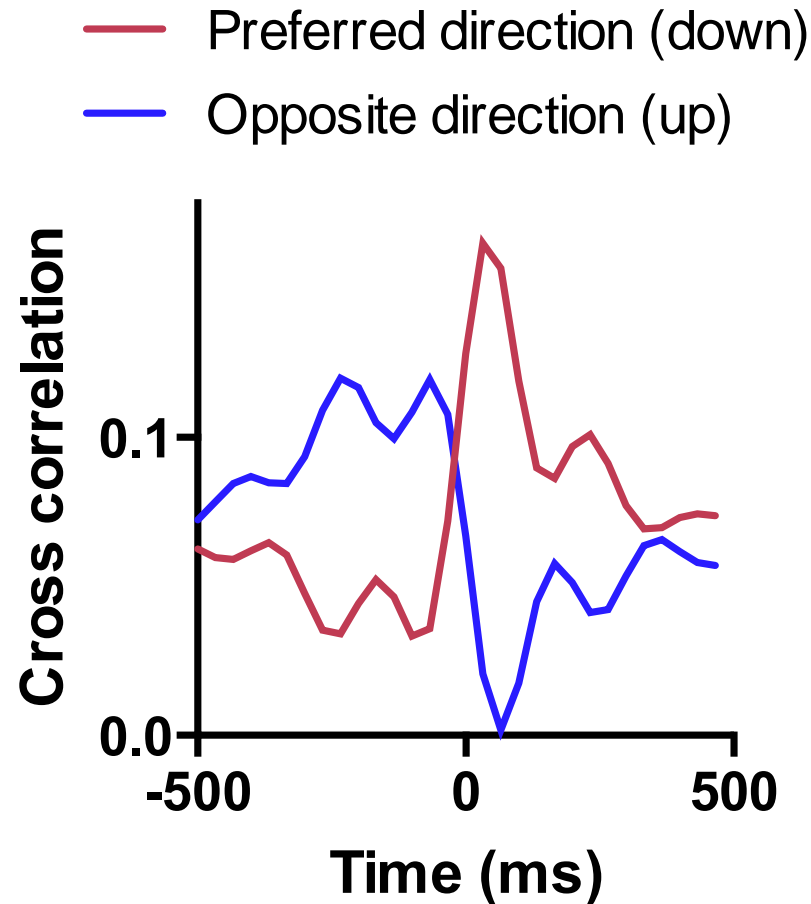
## Dopamine neurons represent movement velocity



# Independent of reward



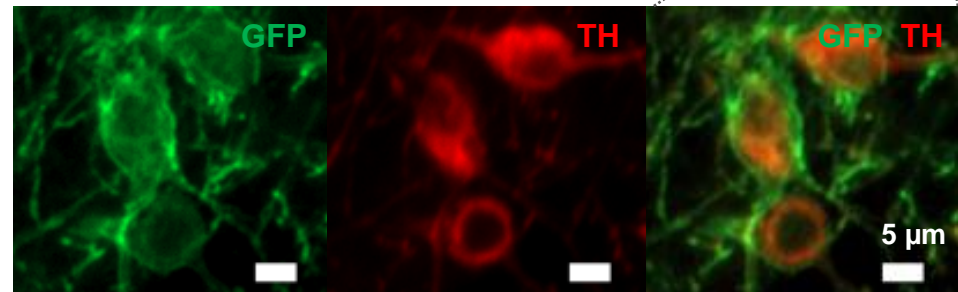
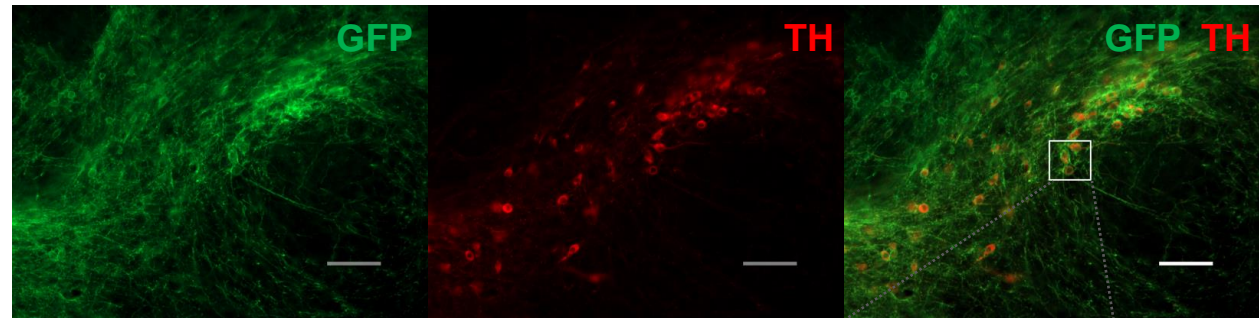
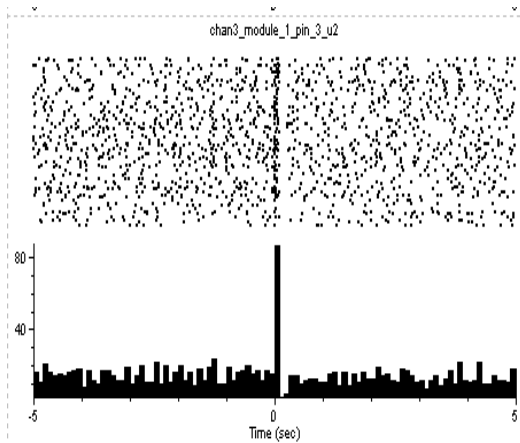
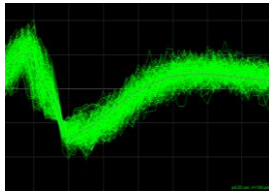
# Direction specific





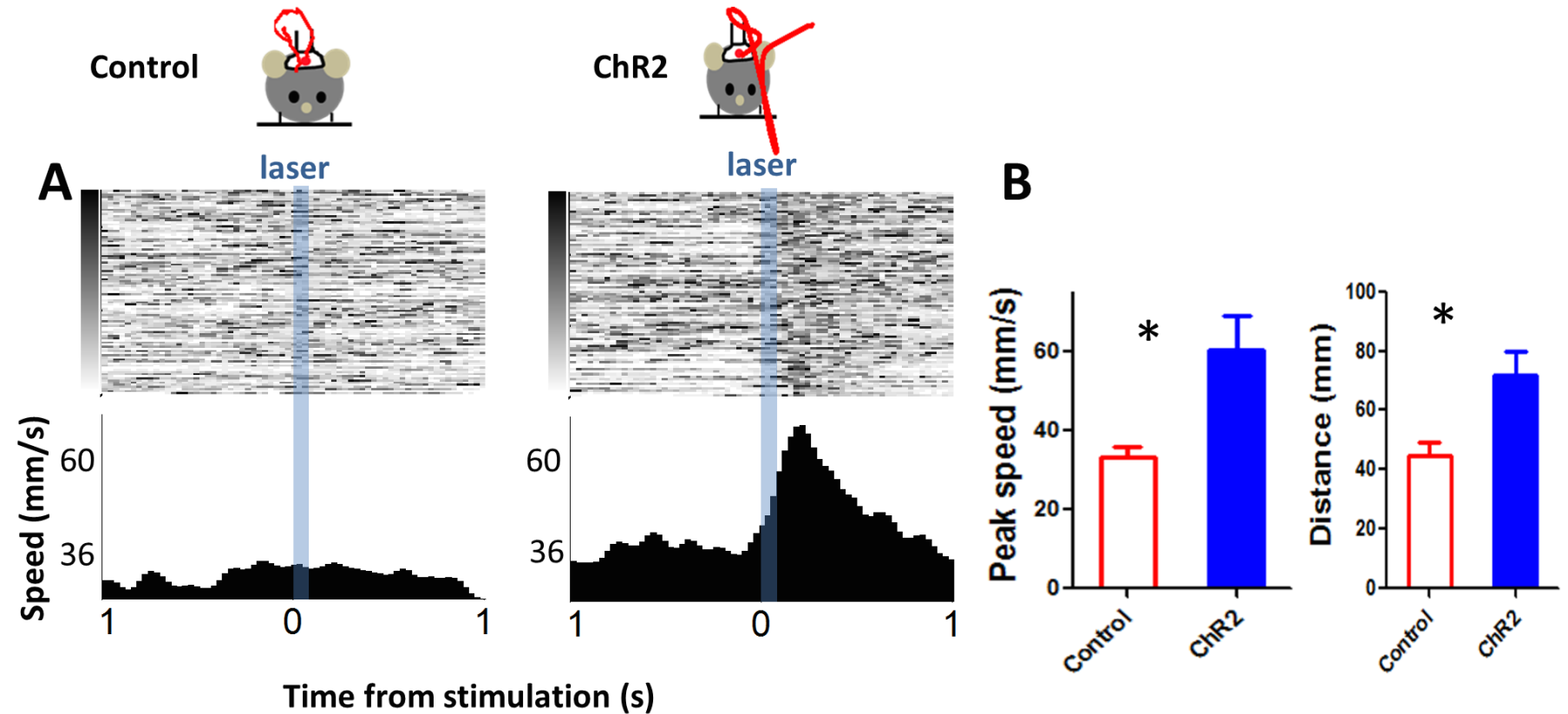
# Stimulating DA neurons

- TH-Cre (tyrosine hydroxylase) x Ai 32 (channelrhodopsin).  
Selectively express ChR2 in DA neurons.

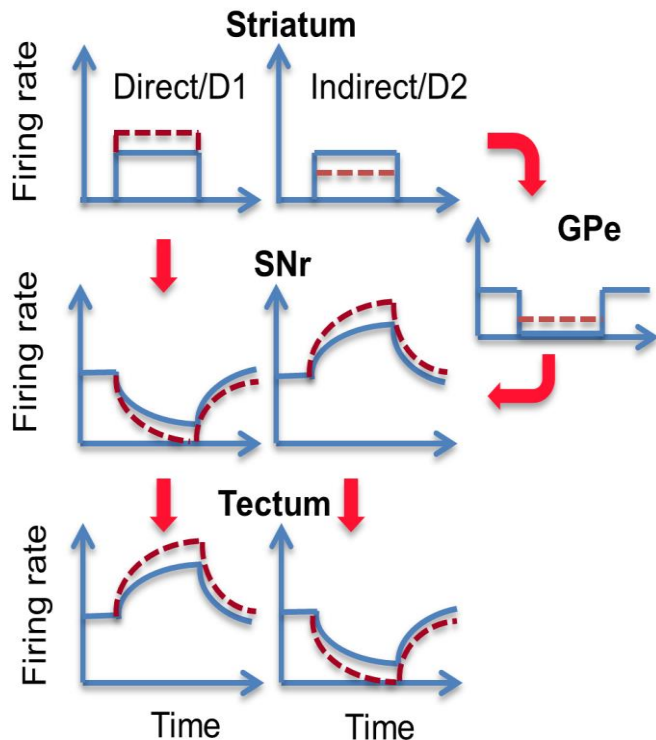


Laser on (blue light)

# Stimulating DA neurons generate movements

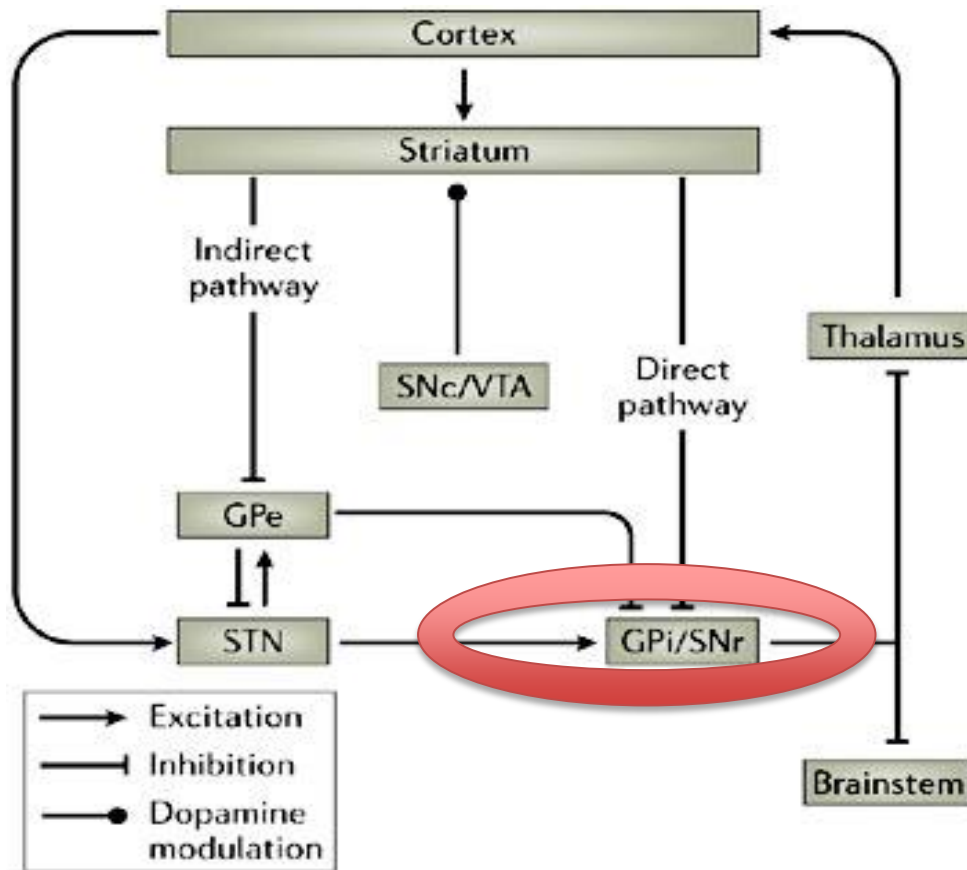


# Summary of dopamine results

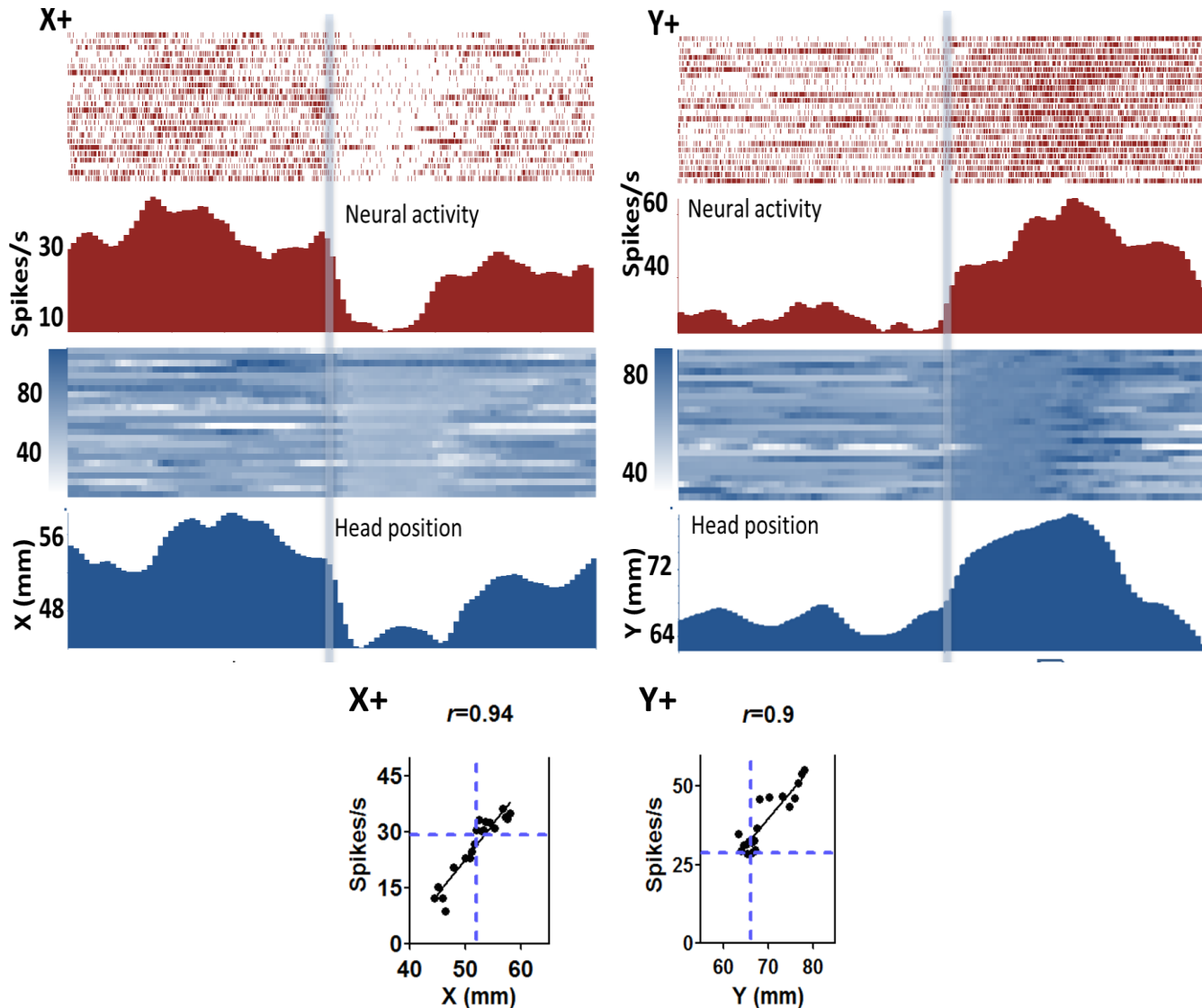


- Dopamine does not encode reward prediction error, but represents movement velocity and acceleration in specific directions.
- Dopamine adjusts gain of the velocity control system by changing the responsiveness of striatal neurons.
- Parkinson's disease: Bradykinesia and akinesia. Slowness of movement reflects reduced velocity error signal.
- Functionally replace dopamine.

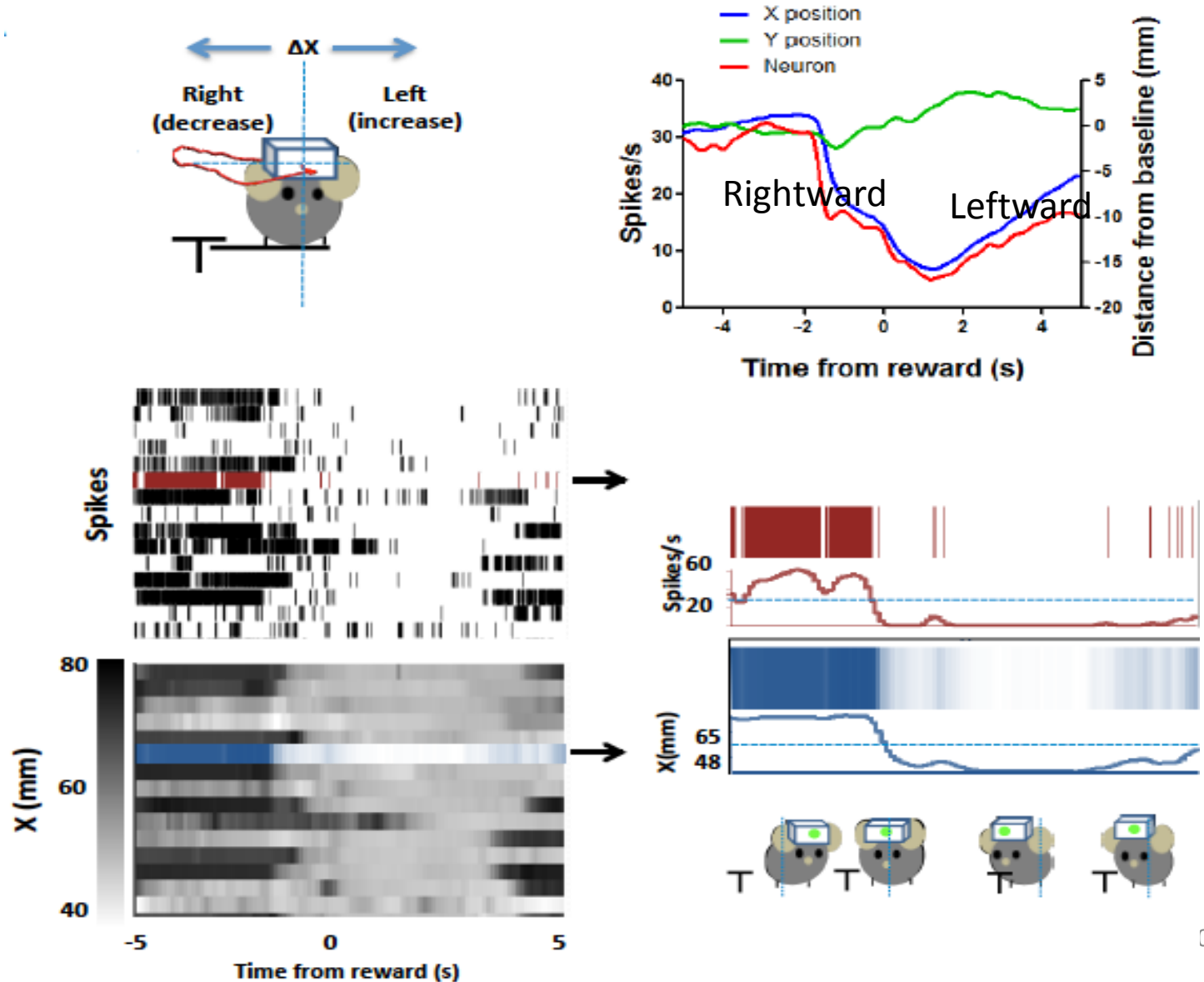
# Single unit recording from the substantia nigra pars reticulata



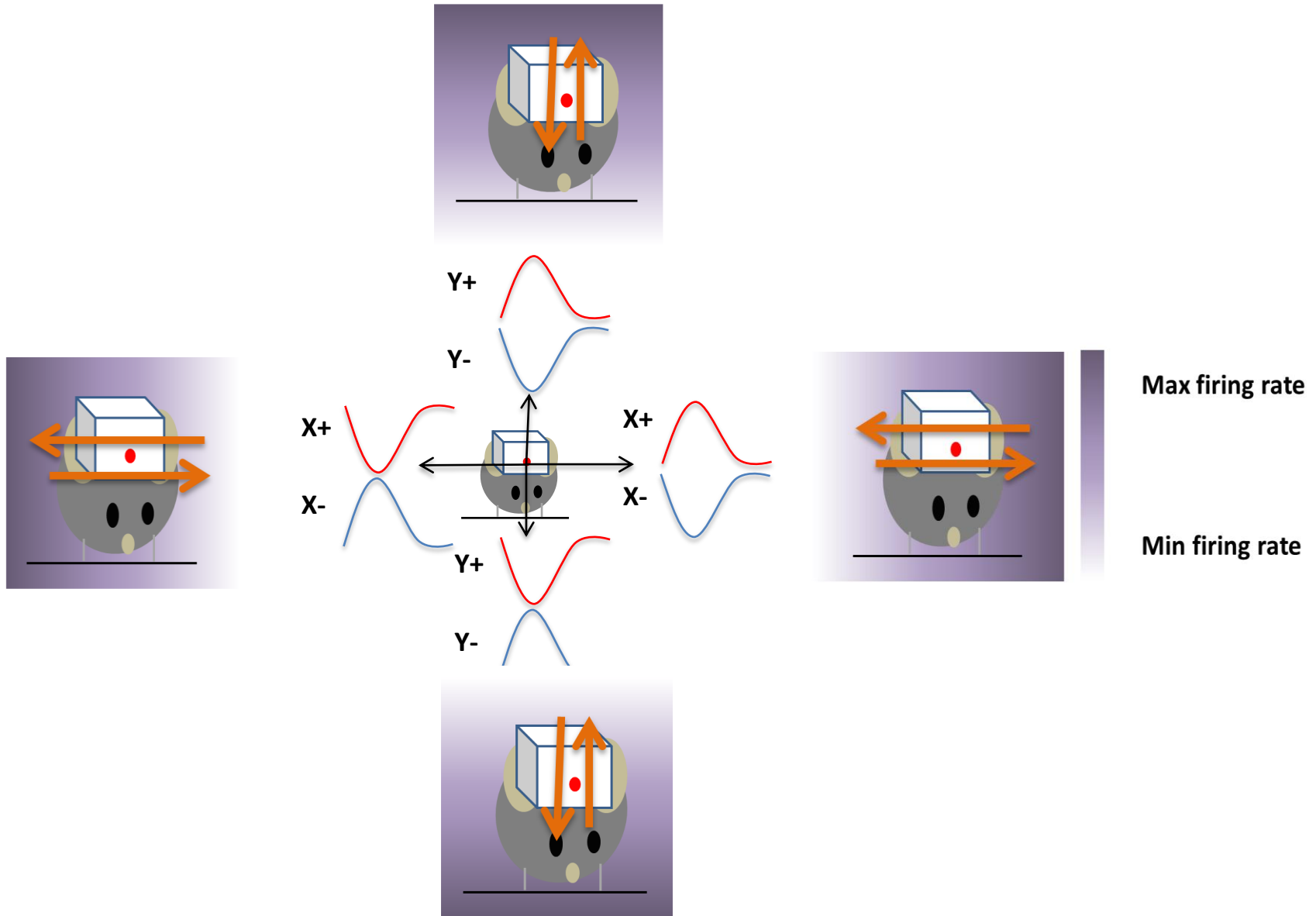
# SNr GABA output neurons signal instantaneous Cartesian position coordinates



# Trial by trial correlations: example X+ neuron (leftward)



# Summary of opponent outputs from SNr



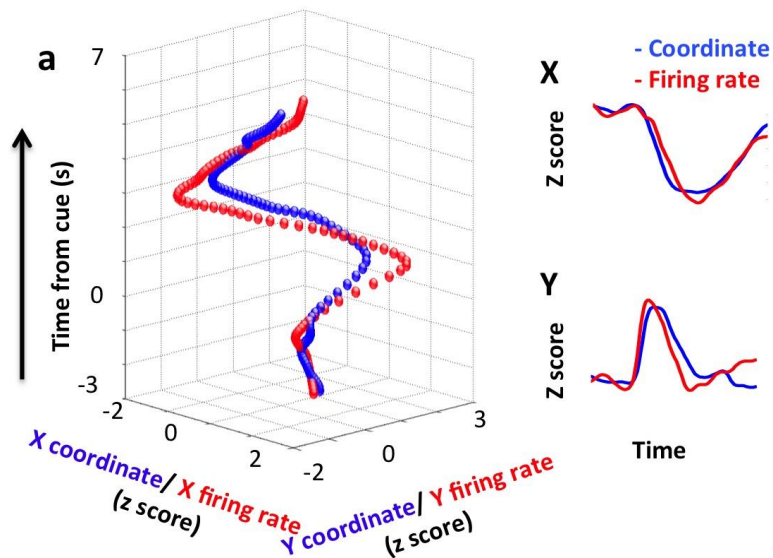
# Summary

- Falsifies rate model of BG, reward prediction error, etc.
- BG output at any time represents position.
- Constant output = stable posture achieved by lower systems.
- Change in output = change in position, i.e. movement.
- Rate of change = movement velocity.

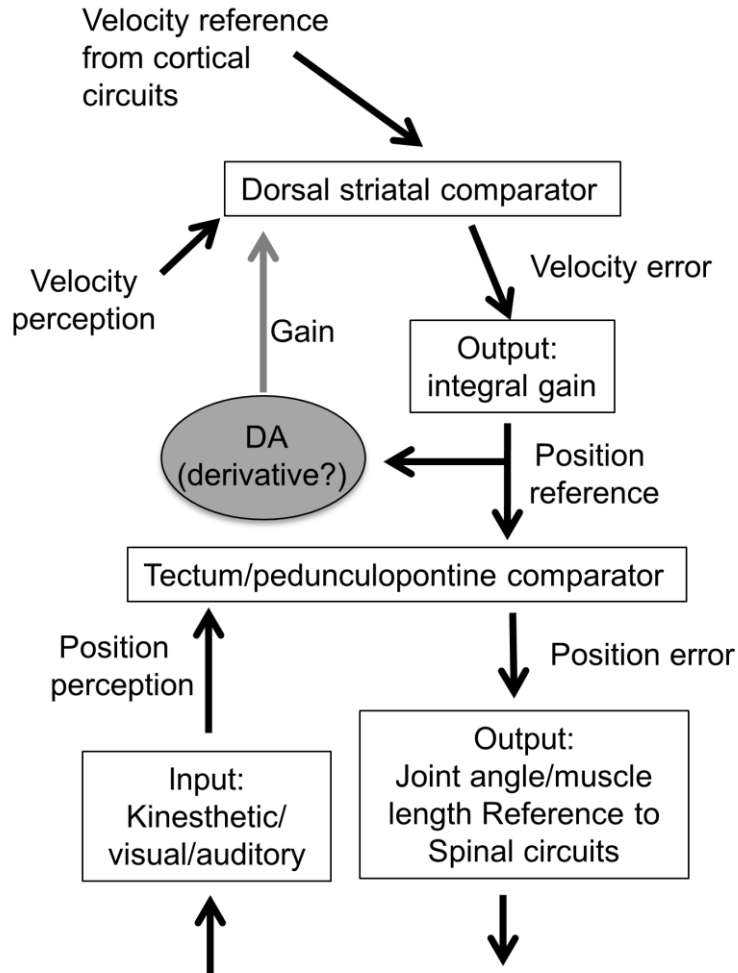


# Position vector from firing rate

In a few hours, one can build a simple mouse robot



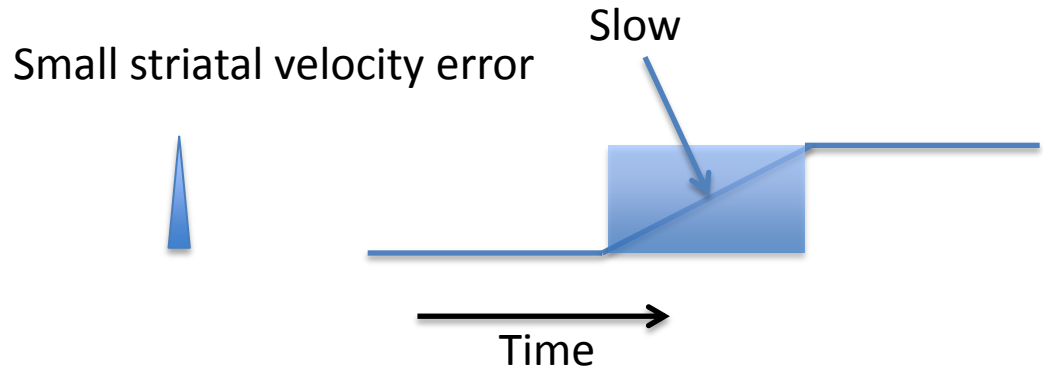
# Cascade control organization



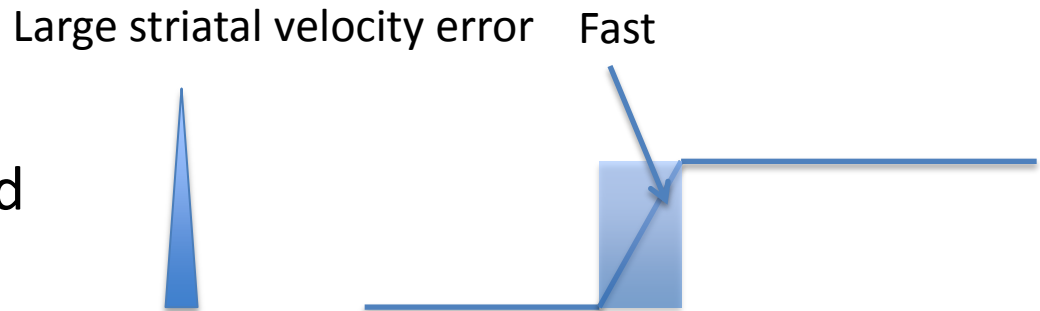
- Cascade control organization: Velocity loop above position loop
- Striatal output (firing rate) reflects velocity. Nigral output reflects position.
- Integration: must convert velocity error into a reference signal for position controller.

# Integral gain

- Rate of change in integral integrator output reflects magnitude of input.



- Sustained output in the absence of error. Position is maintained unless the integrator is discharged.



# Conclusions and implications

- Replace event-based approach with process-based approach.
- By partitioning the world of continuous reciprocal relationships into events, we mask the real processes at work.
- Treating neurological disorders; brain-machine interface; robotics.

# Acknowledgments

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## **Yin lab members**

Joe Barter

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Daniel Salas-Meza

Stephan Castro

Ryan Bartholomew

Yedema Hayrapetyan

Tatyana Sukharnikova

Tyler Shoemaker

Haofang Li

There are statements ... that many basal ganglia neurophysiologists would consider at best highly arguable or just plain wrong.

--Anonymous reviewer 1

Claiming that dopamine signals can reflect 'particular actions' is ... difficult to reconcile with the overwhelming evidence showing no specific movement relationships in dopamine activity.

--Anonymous reviewer 2